INTRODUCTION

Fungal exposure is a daily fact of human existence, which infrequently results in disease. Yet fungal allergy drives asthma severity in very large numbers of people affected by severe asthma. Available statements from different medical associations are unequivocal in declaring that fungi are sensitizers and exacerbate allergic asthma. Modelling suggests that >6.5 million people have severe asthma with fungal sensitizations (SAFS), up to 50% of adult asthmatics attending secondary care have fungal sensitization, and an estimated 4.8 million adults have allergic bronchopulmonary aspergillosis (ABPA) ***(Denning et al., 2014).***

Allergic bronchopulmonary aspergillosis (ABPA) is an immunological pulmonary disorder caused by hypersensitivity to *Aspergillus fumigatus* (*A. fumigatus)*, manifesting with poorly controlled asthma, recurrent pulmonary infiltrates and bronchiectasis ***(Agarwal et al., 2013).*** First described in 1952 by Hinson et al., *A. fumigatus* can complicate the course of disease in patients with asthma and cystic fibrosis (CF) (Hinson et al., 1952). The disease can manifest in childhood and may go unrecognized for years or even decades ***(Agarwal et al., 2010).*** In the last decade, the number of reported ABPA cases have been on the rise, which possibly reflects

heightened physician awareness and the good availability of immunologic assays for the diagnosis of ABPA ***(Al-Mobeireek et al., 2001).***

ABPA is presumed to be primarily a disease of atopic individuals with most of the reported cases occurring in the age group of 20-30 years ***(Kumar et al., 2000).*** ABPA should be suspected in all asthmatics regardless of the severity or the level of control. The importance of recognizing ABPA relates to the improvement of patient symptoms, and delay in development or prevention of bronchiectasis, one manifestation of permanent lung damage in ABPA. Environmental factors may not be the only pathogenetic factors because not all asthmatics develop ABPA despite being exposed to the same environment. As patients with ABPA can be minimally symptomatic or asymptomatic, all asthmatic patients should be routinely investigated for ABPA in secondary care ***(Agarwal et al., 2013).***

The incidence or prevalence of *aspergillus* sensitivity (AS) complicating asthma is unknown owing to the lack of community-based data for this purpose. In asthma and chest clinics, the prevalence of AS is very high. While a recent systematic review reported the prevalence of AS in bronchial asthma to range between 15 and 48% with the pooled prevalence being 28% (95% CI: 24–34), the prevalence of ABPA in chest or asthma clinics was very

high, ranging from 2 to 32% with the pooled prevalence being 12.9% (95% CI: 7.9–18.9) ***(Agarwal et al., 2009).***

The disease remains under-diagnosed in many countries, and as many as one-third are misdiagnosed as pulmonary tuberculosis in developing countries ***(Agarwal et al., 2013).*** In Egypt, no data regarding ABPA prevalence are available, and it is presumed that many cases are unreported. Therefore, the present study was undertaken to find out the prevalence of ABPA in bronchial asthma in all age groups.

Aim of the Work

To detect the prevalence of allergic bronchopulmonary aspergillosis (ABPA) among patients with bronchial asthma.

To study the clinical, radiological, and laboratory profile in these patients.

BRONCHIAL ASTHMA

Definition:

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation ***(GINA, 2014).***

Epidemiology:

Prevalence:

As of 2011, 235–330 million people worldwide are affected by asthma, and approximately 250,000–345,000 people die per year from the disease ***(GINA 2011; Vos et al., 2012).***

Rates vary between countries with prevalence's between 1 and 18%. It is more common in developed than developing countries ***(Murray, 2010).***

One thus sees lower rates in Asia, Eastern Europe and Africa. Within developed countries it is more common in those who are economically disadvantaged while in contrast in developing countries it is more common in the affluent ***(GINA, 2011).***

Allergic diseases and asthma affect an estimated 20% of the population in developed countries ***(Neri and Spanevello, 2000).*** In the European Community Respiratory Health Survey (ECRHS) study, performed in a large cohort of 20-44 year old subjects, the prevalence of asthma was higher in the UK, New Zealand, and the USA and lower in central and southern European countries. These data show a link between the prevalence of asthma and the geographical area or distribution of risk factors ***(Nauta et al., 2008).***

In some populations, the prevalence of diagnosed asthma is still rising, whereas in others it appears to be stable or decreasing slightly. There are no clear differences in trends in prevalence between children and adults, between severe and mild asthma, or between developed and developing countries; however, there are few studies from developing countries ***(Eder et al., 2006).***

Prevalence in Egypt:

The prevalence of asthma among Egyptian children ranges from 3.25% in some studies ***(Massoud et al., 2000)*** to 8% of Egyptian children in others ***(Basilli et al., 1998).*** A study conducted by **Georgy et al., 2006,** using a sample of 2,645 11-15-yr-olds in state and fee-paying schools in Cairo, concluded that prevalence of physician diagnosed asthma in Cairo was 9.4%. They found a higher prevalence

and increased severity of asthma symptoms in children of lower socioeconomic group as defined by state school attendance in Cairo.

Mortality:

In a study; it was found that the overall risk of death from asthma exacerbations in patients 5 yr or older is 0.5%, and was estimated that there were 1,499 hospital deaths in the United States only in 2000 due to asthma ***(Krishnan et al., 2006).***

Asthma Phenotypes:

Asthma is a heterogenous disease with different underlying disease process. Recognizable clusters of demograghic, clinical, and-or pathophysiological characteristics are often called "asthma phenotypes" ***(Bel 2004; Wenzel, 2012).***

In patients with more severe asthma, some phenotypes guided treatments are available. However to do, nostrog relationship had been found between specific pathological features and particular clinical patterns or treatment response. More research is needed to understand the clinical utility of phenotypic classification in asthma ***(Anderson, 2008).***

Many phenotypes have been identified. Some of the most common phenotypes include:

Allergic asthma: is the most easily recognized asthma phenotype which often commences in childhood and associated with a past and/or family history such as eczema, allergic rhinitis or food or drug allergy. Examination of induced sputum of these patients before treatment often reveals eosinophilic airway inflammation. Patient with this asthma phenotype usually respond well to inhaled corticosteroids ***(GINA, 2014).***

Non Allergic asthma: some adults have asthma that is not associated with allergy. The cellular profile of the sputum of these patients may be neutrophilic, eosinophilic or contain only a few inflammatory cells (paucigranulocytic). Patients with non allergic asthma often respond less well to CS ***(GINA, 2014).***

Late-onset asthma: Some adults, particularly women present with asthma for the first time in adult life. These patients tend to be non allergic and often require higher doses of ICS or are relatively refractory to corticosteroid treatment ***(GINA, 2014).***

Asthma with fixed air flow limitation: Some patients with long standing asthma develop fixed airway limitation that is through to be due to airway wall remodeling ***(GINA, 2014).***

Asthma with obesity: Some obese patients with asthma have prominent respiratory symptoms and little eosinophilic airway inflammation ***(Bel, 2004; Wenzel, 2010).***

Steroid-resistant asthma: Glucocorticoids are the mainstay of asthma treatment, but a small subset of patients demonstrates persistent tissue inflammation despite treatment with high doses of inhaled and oral glucocorticoids. Recent studies have greatly improved the understanding of the molecular mechanism whereby glucocorticoids exert their effect. Steroid resistance in asthma is acquired in 95% of the patients, and in itself represents several subtypes, depending on the trigger or genetic background of the host ***(Leung, Bloom 2003).***

Exercise-induced asthma: Exercise-induced bronchoconstriction / exercise-induced asthma (EIB/EIA) has been defined as a fall in FEV1 of 10% or greater on an exercise challenge test (4-6 min of exercise at near-maximum targets with a total duration of exercise of 6-8 min) ***(Godfrey, 1999).*** Pretreatment with any one of the bronchodilator agents (SABA, SAMA, LABA) or anti-inflammatory agents (LTRA, mast cell stabilizers, but not ICS) has been shown to be effective in preventing EIA ***(Dryden,et al 2010; Bonini, 2013).***

Daily use of ICS, LTRA or LABA has also been shown to decrease the fall in FEV1 associated with exercise. However, regular use of LABA can induce tachyphylaxis and may be associated with increased mortality (when used without ICS) ***(Dryden et al,2010; Silvers, 2012; Parsons et al,2013).***

Aspirin-induced asthma (AIA): Aspirin-induced asthma occurs because of the inhibition of the enzyme cyclo-oxygenase 1 (COX-1) by aspirin and other similar non-steroidal anti-inflammatory drugs (NSAIDs) which can cross-react with aspirin ***(*Babu and Salvi 2000*).***

The diagnosis of AIA can be established by oral, nasal or bronchial challenge testing with aspirin in patients with a suggestive history. However, such testing is potentially dangerous as it can produce life-threatening complications. COX-2 inhibitors have been shown to be safe in AIA in numerous studies ***(El Miedany et al , 2006; Woessner,et al 2004).***

Pathophysiology of bronchial asthma:

The pathophysiology of asthma is complex and involves the following components:

- Bronchoconstriction
- Airway inflammation
- Bronchial hyperresponsiveness
- Air way remodeling

Bronchoconstriction:

During an asthma episode, inflamed airways react to environmental triggers such as smoke, dust, or pollen. The airways narrow and produce excess mucus, making it difficult to breathe. In essence, asthma is the result of an

immune response in the bronchial airways ***(Maddox,et al 2002).***

The airways of asthma patients are "hypersensitive" to certain triggers, also known as stimuli. (It is usually classified as type I hypersensitivity). In response to exposure to these triggers, the bronchi (large airways) contract into spasm (an "asthma attack"). Inflammation soon follows, leading to a further narrowing of the airways and excessive mucus production, which leads to coughing and other breathing difficulties. Bronchospasm may resolve spontaneously in 1–2 hours, or in about 50% of subjects, may become part of a 'late' response, where this initial insult is followed 3–12 hours later with further bronchoconstriction and inflammation ***(Murray and Nadel's 2005).***

Airway inflammation

The mechanism of inflammation in asthma may be acute, subacute, or chronic, and the presence of airway edema and mucus secretion also contributes to airflow obstruction and bronchial reactivity. Varying degrees of mononuclear cell and eosinophil infiltration, mucus hypersecretion, desquamation of the epithelium, smooth muscle hyperplasia, and airway remodeling are present ***(Busse et al., 2001).***

Airway inflammation in asthma may represent a loss of normal balance between two "opposing" populations of Th lymphocytes. Two types of Th lymphocytes have been characterized: Th1 and Th2. Th1 cells produce interleukin (IL)-2 and IFN-α, which are critical in cellular defense mechanisms in response to infection. Th2, in contrast, generates a family of cytokines (IL-4, IL-5, IL-6, IL-9, and IL-13) that can mediate allergic inflammation ***(Gauvreau et al., 2011).***

The "hygiene hypothesis" postulates that an imbalance in the regulation of these T_H cell types in early life leads to a long-term domination of the cells involved in allergic responses over those involved in fighting infection. The suggestion is that for a child being exposed to microbes early in life, taking fewer antibiotics, living in a large family, and growing up in the country stimulate the Th1 response and reduce the odds of developing asthma ***(Tippets2009 and Guilbert 2009).***

Asthma is associated with a procoagulant state in the bronchoalveolar space ***(De Boer et al., 2012).***

Bronchial hyper-responsiveness

Hyperinflation compensates for the airflow obstruction, but this compensation is limited when the tidal volume approaches the volume of the pulmonary dead space; the

result is alveolar hypoventilation. Uneven changes in airflow resistance, the resulting uneven distribution of air, and alterations in circulation from increased intra-alveolar pressure due to hyperinflation all lead to ventilation-perfusion mismatch. Vasoconstriction due to alveolar hypoxia also contributes to this mismatch. Vasoconstriction is also considered an adaptive response to ventilation/perfusion mismatch ***(*Global Strategy for Asthma Management and Prevention. NIH Publication; 2008).**

The degree to which airway hyper-responsiveness can be defined by contractile responses to challenges with methacholine correlates with the clinical severity of asthma. The mechanisms influencing airway hyper-responsiveness are multiple and include inflammation, dysfunctional neuroregulation, and structural changes; inflammation appears to be a major factor in determining the degree of airway hyper-responsiveness ***(EPR-3, 2007).***

Air way remodeling:

Airway remodeling as a consequence of inflammation is another characteristic of asthma Structural changes that occur due to inflammation include thickening of the basement membrane, subepithelial fibrosis, goblet cell metaplasia, neovascularization, and increased airway smooth muscle mass ***(Fixman et al , 2007).***

Examination of the relationship between airway remodeling and degree of asthma severity determined that clinical and functional severity scores of asthma were the strongest predictors of increased subepithelial layer thickness, independent of duration of disease, FEV1 This suggests that all patients with severe, poorly controlled asthma can experience deleterious effects on the structure and function of their airways, regardless of the duration of disease ***(Pascual and Peter, 2009).***

While a definitive cause/effect relationship has yet to be conclusively established, airway remodeling has been associated with irreversible decline in FEV1, loss of bronchodilator reversibility, and increased airway hyper-responsiveness ***(Pascual and Peter, 2009).***

IL-33, a member of the IL-1 family, has been implicated in the airway remodeling process. It is produced by airway epithelial cells and smooth muscle cells to stimulate collagen synthesis by fibroblasts, resulting in increased reticular basement membrane thickness ***(Liew, 2012).***

IL-33 is important in switching from Th1 to Th2 responses *in vivo*, producing Th2 cytokines IL-5 and IL-13, as well as inducing cytokine release from mast cells and increasing expression of IL-17 by Th1 cells ***(Fujita, et al 2012).***

The action of IL-33 is unaffected by exposure to high-dose steroids, suggesting that this interleukin plays an

important role in the pathogenesis of steroid-resistant asthma ***(Saglani et al , 2013).***

Factors influencing the development and expression of asthma:

Factors that influence the risk of asthma can be divided into those that cause the development of asthma and those that trigger asthma symptoms. The former include host factors (which are primarily genetic) and the latter are usually environmental factors (Table. 1)

Host Factors: **Genetic**, e.g., ▪ Genes pre-disposing to atopy ▪ Genes pre-disposing to airway hyper-responsiveness **Obesity** Sex
Environmental Factors ▪ Allergens ▪ Indoor: Domestic mites, furred animals (dogs, cats, mice), cockroach allergen, fungi, molds, yeasts ▪ Outdoor: Pollens, fungi, molds, yeasts ▪ Infections (predominantly viral) ▪ Occupational sensitizers ▪ Tobacco smoke ▪ Passive smoking ▪ Active smoking
Air Pollution ▪ Outdoor ▪ Indoor: smoke and fumes from gas and biomass fuels used for heating and cooling, molds, and cockroach infestations
Diet

Table(1): Factors influencing the development and expression of asthma